

Statement of Common Ownership

When the invention of the present application was made, both the present application and the application that subsequently issued as United States Patent 7,378,255, the latter entitled FLUORIMETRIC DETERMINATION OF ANALYTES BY AN INTRAMOLECULAR QUENCHER-FLUOROPHORE CONJUGATE, were either owned by or subject to an obligation of assignment to Roche Diagnostics Operations, Inc., of Indianapolis, Indiana.

Remarks

Claims 1–6, 8–11, and 14 are pending. Claim 7 is canceled herein without admission or prejudice. Claim 1 is presently amended, and claim 14 is new. Support for the amendments can be found in the original specification, for example, in paragraphs [0015]–[0017] and [0019]. No new matter has been entered.

In the response that follows, citations to column and line numbers of United States patents will be expressed in the form “(X:Y)”, where X represents a column number and Y represents a line number.

Double Patenting Rejection and Rejection Under 35 U.S.C. § 102(e)

Claims 1–11 were rejected on the ground of nonstatutory, obviousness-type double patenting as being unpatentable over claims 1–18 of U.S. Patent No. 7,378,255 to Horn et al. (“Horn”). Claims 1–11 were rejected further under 35 U.S.C. § 102(e) as being clearly anticipated by the Horn. Both of these rejections are respectfully traversed.

With regard to the anticipatory rejection, applicants respectfully submit that a rejection solely under 35 U.S.C. § 102(e) is not proper under the present circumstances, wherein claims are rejected on the ground of nonstatutory, obviousness-type double patenting. *See* MPEP 804, in particular Chart II-B. Without admission to the propriety of the double-patenting rejection or of any other rejection, Applicants respectfully submit that only a rejection under 35 U.S.C. § 103(a), based on an assertion that Horn is eligible as § 102(e) prior art, could be proper. Thus, Applicants respectfully request reconsideration.

In the interest of advancing prosecution of the present application, Applicants have filed with this response a “Statement of Common Ownership.” Applicants respectfully submit that this Statement disqualifies the use of Horn as § 102(e)/103(a) prior art against the present

application, despite the difference in inventive entity. 35 U.S.C. § 103(c); *see* MPEP 706.02(1)(3). The Statement of Common Ownership may properly be made by an attorney of record. MPEP 706.02(1)(3).

With regard to the double-patenting rejection, and as applicable to a rejection under 35 U.S.C. § 102(e), the present application is patentably distinguishable over Horn. Specifically, Horn does not enable one of ordinary skill in the art to at once envisage the use of an *N*-oxide of NBD-amine compound as described in formula (I) in a fluorimetric determination. For a generic formula to anticipate a specific compound within the generic formula, one of ordinary skill in the art must be able to “at once envisage” the specific compound. MPEP 2131.02. To “at once envisage” means to be able to draw the structural formula or write the name of each of the compounds included in the generic formula. *Id.* Furthermore,

[w]hen the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated.

Id.; *Ex parte* A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).

Horn discloses a method for detecting an analyte by redox reaction and fluorimetric determination using a redox indicator of a generic formula Q–F, wherein F is a fluorophore group and Q is a quencher group (2:41–50). Horn discloses at least 25 preferred F groups (4:15–28) and at least 19 preferred Q groups (3:62–4:14). As such, even if each of the options for Q and F in Horn described single, unambiguous substituent groups, at least 475 possible compounds Q–F are possible from combining any one Q group with any one F group. Among the preferred F groups is “NBD derivatives” (4:23), and the preferred Q groups “N-oxides.” (3:67–4:2). However, even if a person of ordinary skill in the art would be led by chance or otherwise to choose “NBD derivatives” and “N-oxides” from among these two lists, a molecule of instant formula (I) could not be drawn or named unless the person of ordinary skill selected an

NBD-amine as the specific NBD derivative from among potentially thousands of possibilities. Horn neither teaches nor suggests derivatization of NBD with groups $-NR^1R^2$ at one or more position the 6-membered ring. The person of ordinary skill, therefore, would be unable to “at once envisage” a molecule of instant formula (I) from the disclosure of Horn.

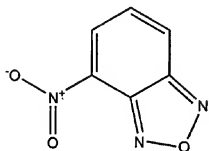
Thus, with regard to double-patenting, the instant claims directed, *inter alia*, to a fluorimetric method employing *N*-oxides of NBD-amines are patentably distinct from the claims of Horn directed to generic formula Q-F. Likewise, with regard to a rejection under § 102(e), the instant claims are not anticipated by any disclosure in Horn. Applicants respectfully traverse these rejections and respectfully request reconsideration.

Rejections Under 35 U.S.C. § 102(b)

Claims 1–3 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Cass et al. (US 6,312,906, “Cass”). Claims 1–11 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Lakowicz (2002/0160400), Albarella et al. (US 6,872,573, “Albarella”), Hoenes (US 5,334,508), or Ghosh et al. (US 4,358,595, “Ghosh”). Applicants respectfully traverse these rejections and request reconsideration.

None of the above references anticipates the claims of the present application, because none of the above references discloses causing a redox reaction between an analyte and a detection reagent comprising an *N*-oxide of an NBD-amine compound of the general formula (I), performing a fluorimetric determination, and detecting the presence of the analyte, as recited in the instant claims. “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Vardegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The present record indicates continuing confusion regarding the identity of the claimed molecules and the distinction between the claimed molecules and "NBD". Applicants respectfully submit the following explanation to clarify this issue:



7-Nitro-benz-2,1,3-oxadiazol

Figure 1: Molecule from "Chemdraw" sketch in file wrapper as "NPL Document" dated July 25, 2006.

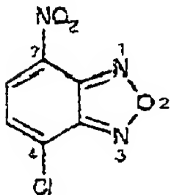


Figure 2: Molecule "NBD-Cl" depicted in Exhibit A of Applicants' Response dated October 3, 2005.

Referring to above Figure 1, during a previous search the Examiner produced the drawing of 7-nitro-benz-2,1,3-oxadiazol. Figure 2 is presented here for the sole purpose of illustrating the numbering scheme for substituent groups of molecules of this kind. It will be apparent that the 7 position of the 6-membered ring is equivalent to the 4 position, and as such the molecule of Figure 1 also could be named "4-nitro-benz-2,1,3-oxadiazol," which Examiner correctly

identified in the office action of February 2, 2009, as “NBD.” Any further mention in this response of “NBD” by itself refers to the molecule shown in Figure 1. Molecules of NBD are characterized by a five-membered oxadiazole ring fused with a six-membered ring and an NO₂ group at either the 4-position or the equivalent 7-position.

An interview summary entered into the present record on June 21, 2006, contains the following comment: “Applicants’ stated . . . 7-nitro-benz-2,1,3-oxadiazol is the name of the claimed chemical structure.” Applicants contradicted the above comment in a subsequent interview, the summary of which was entered April 2, 2007, and also in a response dated April 30, 2007. Specifically, Applicants stated, “Compound I is not 7-Nitro-benz-2,1,3-oxadiazole, but is the N-oxide of NBD-amine or derivatives thereof (see para. [0009]).” Nevertheless, the instant claims stand rejected over references that disclose NBD or NBD derivatives but do not disclose *N*-oxides of NBD-amine or derivatives thereof.

To reiterate, the claimed molecules of formula (I) are *not* NBD, and NBD is *not* a claimed molecule according to formula (I). The following clarification explains the origin of the terminology “*N*-oxide of NBD-amine.”

Figure 3 (below) depicts formula (I) as recited in the instant claims, but with circles drawn around groups distinguishing formula (I) from NBD. The claims recite further that R¹ and R² are each independently selected from R, (CH₂CH₂O)_mR, COR, COOR and OCOR; R³ in each case is independently selected from NO₂, CN, R, OR, OCOR, COOR, SR and halogen; R is H or C₁–C₄ alkyl, where alkyl is optionally substituted with halogen, OR, SR, NR₂, COOR, CONR₂, SO₃R and salts thereof or/and PO(OR)₃ and salts thereof; *m* is an integer from 1–20; and *n* is 1, 2 or 3.

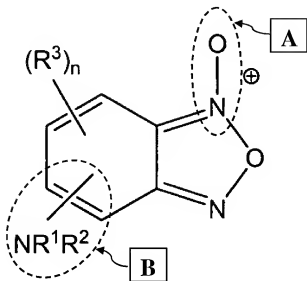


Figure 3: Formula (I) as recited in the instant claims.

Molecules of formula (I) differ from NBD in at least two respects. First, all molecules of formula (I) comprise group A, an *N*-oxide. Evident from Figure 1, NBD lacks an *N*-oxide. Second, the molecule of formula (I) comprises at least one group B, an amine group $-NR^1R^2$. Neither R^1 nor R^2 may be oxygen; thus, NO_2 cannot result from the $-NR^1R^2$ group. NBD both lacks such an amine group and contains an NO_2 group. It is acknowledged that an R^3 group on the 4-position or the 7-position of the claimed molecules may be NO_2 with n equal to 1. However, even if such an NO_2 group were present, the molecule still would contain both the *N*-oxide group (A) and the amine group $-NR^1R^2$ (B), both of which are lacking from NBD. Applicants respectfully submit that there exists no choice for variables R , R^1 , R^2 , R^3 , m , and n that could be made to result in NBD.

In the sense that all molecules of formula (I) contain an amine group $-NR^1R^2$ and NBD always contains an NO_2 group, the amine group of formula (I) effectively *replaces* the NO_2 group of NBD. Therein lay the basis for the terminology throughout the present disclosure that the inventive molecules are *N*-oxides of NBD-amine and derivatives thereof. Further, inconsistent with anticipatory rejections of the instantly claimed molecules over references

disclosing NBD or NBD derivatives, there is no basis for inferring that the name “NBD-amine” implies simply adding an amine group to a molecule of NBD or of an NBD derivative.

For purposes of further clarification only, Figure 4 shows two molecules from the Wang reference cited in a previous IDS. Benzofuroxan is an *N*-oxide. It is not an NBD-amine, for lack of an amine group, and it is not describable by formula (I) of the instant claims. But the molecule 4-aminobenzofuroxan is both an *N*-oxide and an NBD-amine, despite its lack of an NO₂ group. The 4-aminobenzofuroxan could be defined by formula (I), whereby every instance

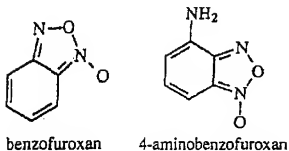


Figure 4: Two molecules depicted in Wang et al., *J. Supercrit. Fluids*, 1995, **8**, 236–249, of record as NPL document dated July 19, 2004.

of R¹, R², and R³ would be hydrogen, and every instance of *n* would be 2. To note, if the NH₂ group of 4-aminobenzofuroxan were to be replaced with NO₂, the resulting molecule would be an *N*-oxide of **NBD**, but not an *N*-oxide of **NBD-amine**. Such a molecule would not be definable by formula (I), because the molecule would lack at least one amine group NR¹R².

The Cass reference discloses a method of detecting a biological analyte using NBD as an indicator. (8:38) As has been explained in detail above, NBD is not an indicator that can be defined by formula (I) of the instant claims. Furthermore, the detection method taught by Cass involves ascertaining a change of distance between the fluorescent group and the carrier surface quenching the fluorescent emission (4:49–66 and Fig.2). As such, Cass does not disclose a method comprising causing a redox reaction, particularly by contacting a sample containing an analyte with a detection reagent comprising an *N*-oxide of an NBD-amine of formula (I). Thus,

Cass does not disclose each and every element of instant claims 1 and 14, and all claims dependent thereon.

The Lakowicz reference discloses in paragraph [0066] a fluorescent detection method involving “7-nitrobenzo-2-oxa-1,3-diazol-4-yl-chloride” (NBD-Cl, not “NBD” as stated in the office action of February 2, 2009). The NBD-Cl is the molecule depicted in Figure 2, above. Like NBD, NBD-Cl lacks both the *N*-oxide and the NR^1R^2 group that are necessary components of all molecules of formula (I) of the instant claims. As such, Lakowicz does not disclose a method comprising a redox reaction between an analyte and an *N*-oxide of an NBD-amine. Thus, Lakowicz does not disclose each and every element of instant claim 1, and all claims dependent thereon.

Regarding the Hoenes reference, in the office action of July 25, 2006, it was stated, “The Office agrees Hones [*sic*] fails to disclose the claimed method and only the composition claims have been rejected over Hones [*sic*].” The composition claims were canceled in a previous response. Amendments on the record since July 25, 2006, have distinguished the claimed method even further from Hoenes than it was in 2006. Though the Office already has stated that Hoenes fails to disclose the presently claimed method, Applicants respectfully resubmit that Hoenes discloses methods for *colorimetric* determination of analytes, not for *fluorimetric* determination. Colorimetric methods and fluorimetric methods proceed by entirely different physical mechanisms. Though Hoenes discloses *N*-oxides of benzofuroxan (e.g., at 5:36—6:15 and Example 1), the 6-membered rings of the benzofuroxans are substituted only with lower alkyl, lower alkoxy, lower alkylcarbonyl, or formyl residues. Hoenes does not disclose substituting the 6-membered ring of the benzofuroxan with a group $-\text{NR}^1\text{R}^2$, as required in formula (I) of the instant claims. As such Hoenes fails to disclose both a fluorimetric detection method and any detection method involving *N*-oxides of NBD-amine. Thus, Hoenes does not disclose each and every element of instant claims 1 and 14, and all claims dependent thereon.

The Albarella reference discloses a method for detection of creatine using generically described 4-(1-alkylhydrazino)-7-substituted benzoxadiazol (MNBDH) as a detection reagent. The MNBDH fluoresces when it is oxidized, and the fluorescence is detected. Though these molecules could be called “NBD-amines” according to the terminology of the present disclosure, nowhere does Albarella disclose that the generic MNBDH contain an *N*-oxide. Thus, Albarella fails to disclose each and every element of claim 1 and all claims dependent thereon. Furthermore, in the method taught by Albarella, the MNBDH is always oxidized and the analyte is always reduced. (Abstract, 3:5–11). As recited in instant claim 14, *N*-oxides of NBD-amine are reduced during the redox reaction and the analyte is oxidized to produce a detectable fluorescence signal. Thus, Albarella fails to disclose each and every element of claim 14.

The Ghosh reference discloses 4-chloro-7-sulfobenzofurazans as analogues of 4-chloro-7-nitrobenzofurazan (NBD-Cl). Except for the NBD-Cl in the background section, all compounds disclosed in Ghosh contain neither an *N*-oxide nor an amine group NR^1R^2 . The NBD-Cl has been addressed above from the Lakowicz reference. Also, instant formula (I) contains no means for bonding an SO_3^-M^+ group to the 6-membered ring. Ghosh lacks further any disclosure of a redox-driven fluorimetric determination. Rather, Ghosh discloses only a chromatographic determination. Thus, Ghosh fails to disclose each and every element of claims 1 and 14, and all claims dependent thereon.

None of the cited references discloses a fluorimetric determination method comprising the use of a detection reagent comprising an *N*-oxide of NBD-amine of formula (I), particularly with further enzymes for catalyzing the reduction or oxidation of an analyte and the compound of formula (I), as recited in instant claim 1. Furthermore, none of the cited references discloses a reduction of the detection reagent, as recited in instant claim 14.

For the above reasons, all the cited references fail to disclose each and every element of claims 1 and 14, and all claims dependent thereon. Therefore, Applicants respectfully traverse

the rejections under § 102(b) and respectfully request the Examiner to reconsider and withdraw the rejections.

Conclusion

Applicants respectfully submit that the present application is in condition for allowance. The Examiner is encouraged to contact the undersigned to resolve efficiently any formal matters or to discuss any aspects of the application or of this response.

Respectfully submitted,

DINSMORE & SHOHL L.L.P.

By /Richard J. McNeely/
Richard J. McNeely
Registration No. 59,149

One Dayton Centre
One South Main Street, Suite 1300
Dayton, Ohio 45402-2023
Telephone: (937) 449-6400
Facsimile: (937) 449-6405
e-mail: richard.mcneely@dinslaw.com